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Epigenetic Control of Oligodendrocyte Development: Adding New Players to Old Keepers

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Abstract

Emerging and strengthening evidence suggests an important role of myelin in plasticity and axonal survival. However, the mechanisms regulating progression from oligodendrocyte progenitor cells (OPCs) to myelinating oligodendrocytes remain only partially understood. A series of overlapping yet distinct epigenetic events occur as a proliferating OPC exits the cell cycle, initiates differentiation, and becomes a myelin-forming oligodendrocyte that wraps axons. Here we discuss recent advances towards understanding the epigenetic control of oligodendrocyte development that integrates environmental stimuli. We suggest that OPCs are directly responsive to extrinsic signals due to predominantly euchromatic nuclei, while the heterochromatic nuclei render differentiating and myelinating cells less susceptible to signals modulating the epigenome.

INTRODUCTION

Oligodendrocytes provide metabolic support and insulation to axons of the CNS, and are responsive to environmental activity [1-6]. Oligodendrocytes are generated from proliferating oligodendrocyte progenitor cells (OPCs). Upon extracellular signals, OPCs differentiate into post-mitotic premyelinating oligodendrocyte and subsequently myelinate adjacent axons. This process is driven by the interplay of extracellular signals with intrinsic molecular components, in which epigenetic regulation plays a fundamental role in governing the accessibility of transcriptional machinery to DNA sequences, and comprises DNA and histone modifications, histone variants, ATP-dependent chromatin remodeling complexes, microRNAs, and long intergenic non-coding RNAs (lincRNAs). This review focuses on recent advances in understanding epigenetic control leading to both transcriptional repression and activation during oligodendrocyte development. We discuss the potential

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Conflict of interests

All authors declare no conflict of interests.

mechanisms by which environmental signals are transduced into intracellular actions through epigenetic modifications, and how this process is disrupted in neurologic diseases.

Epigenetic changes resulting in transcriptional repression during oligodendrocyte development

OPCs derive from multipotential neuroectodermal derivatives and are characterized by expression of molecules regulating migration and proliferation, and lack expression of myelin [7,8] and pluripotency [9] genes. At the ultrastructural level, OPCs exhibit euchromatic nuclei, defined by a relaxed chromatin structure and easy DNA accessibility. Therefore, OPCs can transduce extracellular signals to transcription factors, which often recruit large protein complexes containing co-activators or co-repressors and histone-modifying enzymes to accessible DNA sequences, allowing for the transcriptional activation or repression of genes regulating lineage determination, proliferation, and migration. The transition from OPC to premyelinating oligodendrocyte is initiated by downregulation of genes involved in proliferation and inhibition of differentiation. This process is characterized by progressive heterochromatin formation [4], starting at the nuclear periphery, where the nuclear lamins are localized, and radially converging towards the nuclear center.

A large body of evidence supports a model where histone deacetylase (HDAC) activity is necessary in the premyelinating stage to remove the inhibitory “brakes” on myelin gene expression [10-12]. For instance, HDAC1 and HDAC2 were shown to compete with beta-catenin for TCF7L2 interaction to repress Wnt target genes, thereby allowing oligodendrocyte differentiation [12]. During the early differentiation stage, TCF7L2 interacts with a transcriptional corepressor Kaiso/Zbtb33 to block beta-catenin signaling, whereas during maturation, TCF7L2 recruits and cooperates with SOX10 to promote myelination [13]. Thus, TCF7L2 utilizes coregulators in a stage-specific manner to coordinate the activation or repression of transcriptional events.

Silencing of pluripotency and neuronal-lineage genes remains constant throughout differentiation, and has been attributed to the activity of the histone methyltransferases [14,15], including EZH2, a polycomb protein family member, which deposits triple methyl groups on lysine residue K27 of histone H3 (H3K27me3), and other histone methyltransferases that target K9 (H3K9me3). Genome-wide studies using neonatal OPCs found EZH2 occupancy at pluripotency gene loci and certain genes determining neuronal and astrocytic lineage [16], which was further confirmed by a recent study characterizing the presence of H3K27me3 and H3K9me3 at these loci [15]. Interestingly, there are very few genes that share H3K27me3 and H3K9me3 marks in OPCs and premyelinating oligodendrocytes [15], suggesting they play overlapping yet unique repressive roles. While the initial loss of neurogenic ability as neural stem cells transition into OPCs is likely established via repression mediated by H3K27me3 [14,16], H3K9me3 serves as the predominant repressive mechanism for subsequent transition into premyelinating oligodendrocytes [15]. An exception to this is observed with myelin genes, which can be found in a “bivalent” state with coexisting H3K27me3 and H3K4me3 marks. This dual code defines a state of transcriptional competence that prevents myelin genes from being

inappropriately expressed, but allows them to remain “poised” for subsequent activation upon differentiation [8].

DNA methylation is a traditional yet new epigenetic player in oligodendrocyte development. Dynamic expressions of DNA methyltransferases and ten-eleven translocation enzymes (TETs) in the oligodendroglial lineage suggested that DNA methylation and hydroxymethylation are essential for oligodendrocyte differentiation [17,18]. Indeed, TET1, TET2, and TET3 have been shown to be necessary for oligodendrocyte differentiation *in vitro* [18]. Recently, a whole-genome transcriptome and methylome analysis comparing OPCs and oligodendrocytes revealed that DNA methylation is inversely correlated with gene expression during developmental myelination. However, new data show that reduction of DNA methylation via genetic ablation of *Dnmt1* in OPCs is not sufficient to induce differentiation, but rather results in severe hypomyelination of the CNS associated with aberrant alternative splicing events and activation of an ER stress response [19]. This suggests that DNA methylation acts as a regulator of the OPC state and subsequent transition into differentiating oligodendrocytes.

Regulation from non-coding RNAs, including microRNAs and lincRNAs, is more discrete, targeting expression at the transcript level. miR-23 was recently found to enhance oligodendrocyte differentiation by negatively regulating phosphatase and tensin homolog on chromosome 10 (*Pten*) via the activation of a lincRNA *2700046G09Rik* [20]. In addition, miR-23 suppresses expression of the nuclear envelope protein lamin B1, the overexpression of which leads to perturbation of nuclear membrane structure, chromatin organization, and oligodendrocyte differentiation and myelination [21-24]. *OLMALINC* (oligodendrocyte maturation-associated long intervening non-coding RNA) is a recently identified primate-specific lincRNA that is highly expressed in the white matter of the human frontal cortex [25]. Knockdown of *OLMALINC* in human oligodendrocyte cell lines upregulates inhibitors of oligodendrocyte differentiation, including genes regulating maintenance of cytoskeleton structure, cellular adhesion, and membrane signaling. These recent studies suggest the importance of coordination of protein and non-coding RNAs in oligodendrocyte maturation, particularly in the myelin maintenance stage. However, the *in vivo* relevance of non-coding RNAs in oligodendrocyte development remains to be further determined.

Epigenetic changes resulting in transcriptional activation during oligodendrocyte development

Much less is known about epigenetic regulation that leads to transcriptional activation during oligodendrocyte differentiation. OPCs are characterized by their competence of generating multi-lineage cells in addition to oligodendrocyte. A recent study using genome-wide analysis combined with fate mapping revealed that HDAC3 competes with STAT3 for p300, a histone acetyltransferase, to activate expression of oligodendrocyte lineage-specific genes, such as *Olig2*, while repressing astrocyte lineage-specific genes, such as *Nfia* [26].

The limited accessibility of DNA sequences to transcription factors within the nuclei of differentiating oligodendrocytes restricts their responsiveness to extracellular signals. However, access to specific binding sites can be provided via displacement of nucleosomes by ATP-dependent chromatin remodeling complexes. Chromatin immunoprecipitation-

sequencing (ChIP-seq) analysis with RNA polymerase II identified *Smarca4/Brg1*, which encodes the central catalytic ATPase subunit of the SWI/SNF chromatin-remodeling complex, as the most significant target during the initiation of oligodendrocyte differentiation [27]. Furthermore, BRG1 chromatin remodeler is prepatterned with OLIG2 to facilitate expression of oligodendrocyte lineage-specific genes [27], functioning as a feed-forward loop, as the OLIG2/BRG1 complex further targets another chromatin remodeling enzyme, the ATP-dependent chromodomain helicase DNA-binding protein 7 (*Chd7*). Genome-wide mapping of CHD7 target sites revealed that CHD7 forms complexes with SOX10 to activate positive regulatory oligodendrocyte genes, thereby initiating the myelination program [28]. Interestingly, BRG1-dependent chromatin remodeling is dispensable during the later stage of oligodendrocyte maturation, as *Brg1* deletion following lineage specification did not affect OPC proliferation, migration, or survival, with only a mild defect in differentiation [29]. These studies support the concept that once differentiation initiates heterochromatin formation, the increased difficulty for transcription factor to access DNA would require additional involvement of molecules that can recognize, bind and modify histones or DNA in order to allow changes in chromatin conformation, preceding changes in gene expression. This further implies that modulation of molecules that alter chromatin conformation could have a significant impact on oligodendrocyte differentiation. For example, BRD4, a representative member of the BET (bromodomain and extraterminal domain) family of proteins, has two tandem bromodomains (BrD1 and BrD2), which bind histone acetyl-lysines. Interestingly, chemical inhibition of one of these domains (BrD1) was shown to accelerate OPC differentiation, whereas inhibition of both bromodomains blocked differentiation [30], demonstrating the intricate complexity of this process.

Epigenetic changes in oligodendrocytes following environmental signals

Emerging evidence shows that oligodendrogenesis and myelination are affected by underlying changes in neuronal activity [3-6,31]. For example, increases in cortical activity, such as in mice learning to run on a complex wheel, stimulate OPC proliferation and oligodendrogenesis [6]. Moreover, direct optogenetic stimulation of premotor cortical neurons also induces OPC proliferation, differentiation, and increased myelin thickness [3]. The concurrent activity-dependent increase in H3K9me3 and decrease in H3 acetylation that was observed suggests the initiation of a differentiation program through epigenetic mechanisms. Conversely, oligodendrocyte gene expression is downregulated in the prefrontal cortices of mice following social deprivation, which may reduce activity in this area, resulting in hypomyelination [4,5,32]. Importantly, impaired myelination was associated with delayed OPC differentiation and reduced heterochromatin formation [4].

How neuronal activity regulates oligodendrogenesis and myelination remains incompletely understood. Recent studies using zebrafish have shown that synaptic vesicle release regulates the myelination capacity of individual oligodendrocytes [33], and that activity-dependent vesicle release determines the frequency and stability of myelin sheaths on individual axons [34]. However, not all myelination are activity-dependent, as myelination on axons of some neuronal subtypes is insensitive to vesicle release, suggesting the diversity in regulation of myelination [35], OPCs themselves exhibit electrical properties, and the

expression of genes encoding ion channels and neurotransmitter receptors are regulated by the deposition of H3K9me3 during differentiation [15]. Furthermore, silencing of H3K9 methyltransferases increases the electric excitability of immature oligodendrocytes, and inhibits their differentiation. Activity of ion channels and neurotransmitter receptors in OPCs may, in turn, activate epigenetic programs. For instance, the muscarinic receptor antagonist clemastine has been shown to promote OPC differentiation and remyelination *in vivo* [32,36]. Furthermore, clemastine was capable of activating H3K9 methyltransferases *in vitro* in the absence of neuronal or astrocytic signals[32], suggesting the direct activation of the epigenetic program upon receptor signaling.

Other sources of extracellular signals, such as spatial constraints and the stiffness of the extracellular matrix, have recently been shown to directly modulate OPC migration, proliferation, and differentiation [37-40]. For example, plating OPCs at a high density promotes their differentiation, an effect that mainly depends on spatial constraints rather than intercellular interactions, as culturing progenitors at a normal density with inert microspheres also promotes myelination [40]. In addition, increasing the substrate stiffness enhances differentiation of OPCs, whereas optimal levels of proliferation and migration occur within the physiologic ranges of stiffness [39]. How are mechanical signals translated into changes in gene expression? One potential mechanism is that mechanical signals modulate the actin cytoskeleton and nuclear structure of oligodendrocytes [38]. This mechanotransduction involves direct force transition from the cytoplasmic membrane to the nucleus via linker of the nucleoskeleton and cytoskeleton complex (LINC) signals, and also results in deposition of repressive histone marks [38], suggesting a direct interplay of mechanical forces with epigenetic machinery.

Epigenetic regulation is disrupted in pathologic states

Based on what is currently known, it reasons that a disrupted epigenetic state would be present in oligodendrocytes in conditions characterized by a decreased ability to repair myelin, such as multiple sclerosis (MS). Indeed, a recent study combining transcriptomic analysis with whole-genome bisulfite sequencing revealed genome-wide differences in DNA methylation in the normal appearing white matter of MS patients [41]. Genes known to regulate oligodendrocyte survival were hypermethylated and downregulated, whereas genes implicated in proteolytic processing were hypomethylated and upregulated, suggesting there are epigenomic changes affecting oligodendrocyte susceptibility to damage in these patients.

Among the various laminopathies, which are hereditary diseases resulting from mutations in genes encoding the nuclear lamina or lamina-associated proteins [42], myelination is impacted only in adult-onset autosomal dominant leukodystrophy (ADLD). This disease characterized by myelin loss in adults and represents a defect in myelin maintenance that is caused by duplication of *LMNB1* [20,21]. Recent studies show that *Lmnbl* is normally downregulated during oligodendrocyte differentiation, and is kept under tight translational control by miR-23 [21,23]. ADLD can be modeled in mice by overexpression of *Lmnbl* specifically in oligodendrocytes [24]. In this model, degeneration is mediated by a decrease in lipogenic gene expression and subsequent reduction in myelin-enriched lipids, which is concurrent with alterations in histone modifications favoring transcriptional repression.

Perturbed epigenetic regulation in oligodendroglial cells is not limited to demyelinating diseases. Rett syndrome is a neurodevelopmental disorder caused by *de novo* mutations in *MECP2*, which encodes a methyl CpG binding protein. Mutation of *Mecp2* in mice has also been shown to affect oligodendrocytes, which participate in disease progression [43]. Silencing *Mecp2* *in vitro* leads to upregulation of myelin gene expression, though the exact mechanisms require further investigation [44].

CONCLUDING REMARKS

This review discusses recent evidence concerning how extrinsic signals initiate, modify, and stabilize epigenetic changes during oligodendrocyte development and myelin maintenance (Fig.1). It is well documented that demyelinating lesions in the CNS are surrounded by OPCs with high levels of transcriptional inhibitors for differentiation. Therefore, strategies targeting remyelination would require use of epigenome-modulating compounds that either limit the access of transcription factors to the easily accessible DNA in OPCs, or overcome the inaccessibility of myelin genes in heterochromatic DNA in differentiation oligodendrocytes.

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HIGHLIGHTS

- Most epigenetic events regulating OPC differentiation repress transcription.
- Extrinsic cues initiate epigenetic changes in OPCs leading to differentiation.
- Epigenetic regulation in oligodendrocytes is disrupted in disease states.

Fig. 1. Epigenetic control of oligodendrocyte progenitor cell differentiation.

Extracellular signals, including secreted molecules, neuronal activity, and spatial constraints, initiate epigenetic events that either activate or repress transcriptional activity. This leads to repression of alternative lineage-choice genes, as well as genes inhibiting differentiation, followed by activation of myelin genes. CHD7; chromodomain helicase DNA-binding protein 7; DNMT1, DNA methyltransferase 1; HMTs, histone methyltransferases; LINC, linker of the nucleoskeleton and cytoskeleton.